
Natural history of food allergy in infants and children in Israel

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Background: Knowledge about the natural history of food allergy, especially sesame, is scarce.

Objective: To follow the natural history of food allergies in Israel, particularly of sesame allergy.

Methods: The survey was conducted based on clinical records and a detailed questionnaire of children diagnosed as having food allergy.

Results: We found 234 children with suspected food allergy. Testing detected 283 allergies in 180 patients (77%) with confirmed diagnosis. The most common allergies were to cow's milk ($n = 125$), eggs ($n = 71$), sesame ($n = 30$), and soy ($n = 23$). Of those with milk allergy, 69% were IgE mediated (group 1) and 31% were non-IgE mediated (group 2). Group 1 was more likely to have an atopic background than was group 2 ($P = .003$), whereas group 2 was more likely to have resolution of the allergy (35 of 39 [90%] in group 2 compared with only 32 of 86 [37%] in group 1, $P < .001$). Allergy to soy was found in 23 children, of whom 87% manifested with gastrointestinal symptoms and 21 (91%) were also allergic to cow's milk. In 19 children (83%), the allergy resolved. Thirty children had allergy to sesame, and 73% of them had an atopic background. The allergy resolved in only 9 of these patients (30%) at a mean age of 2.8 years.

Conclusions: The distribution of food allergens in Israel differs from that in other countries. Non-IgE-mediated food allergy and particularly milk and soy allergy were likely to resolve completely with time. Sesame allergy was 1 of the most frequent in this cohort, was usually IgE mediated, and tended to resolve in only a few patients.

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INTRODUCTION

Food allergy is common in infants and children. During the past few decades, the prevalence of food allergy has increased, particularly in developed countries. The peak prevalence of food allergy is estimated to be 2% to 8% at 1 year of age; it then decreases progressively until late childhood, after which the prevalence remains stable at approximately 1% to 2%.^{1–3} In contrast, as many as 35% of parents report the presence of allergy or adverse reaction to foods in their children, underlining the importance of definitive evaluation and diagnosis when studying this subject.^{4,5}

In principle, any food may cause an allergic reaction; in practice, most reported food-allergic reactions in the pediatric population are accounted for by cow's milk,⁶ eggs,⁷ peanuts, tree nuts, soy, fish, and wheat.^{3,8} The order of importance of specific allergens varies in different countries, reflecting a possible interaction with dietary habits. For example, peanut allergy is common in North America,^{9–11} fish allergy is common in Spain and Portugal,¹² and sesame allergy is more

prevalent in Israel.¹³ We previously reported¹⁴ that sesame is a major cause of IgE-mediated food-allergic reactions in Israel. In fact, sesame was found to be the third most common allergen and second only to cow's milk as a cause of anaphylaxis.¹⁴

The natural history of many allergenic foods has been previously described. However, even for the most common food allergy, IgE-mediated cow's milk allergy (CMA), there is a wide spectrum of reported tolerance, ranging from only 19% at 4 years of age¹⁵ to 75% at 3 years of age.¹⁶ In time, most food allergies are lost, although allergies to certain foods are long-lived. Food allergens, such as cow's milk, soy, wheat, and eggs, are generally outgrown, whereas most peanut, tree nut, fish, and seafood allergies are persistent.¹⁷ Little is known about the natural history of sesame allergy. The aim of this study is to follow the natural history of food allergies in Israel, particularly of sesame allergy.

MATERIALS AND METHODS

Between May 1, 2000, and March 31, 2006, infants and children referred to the Pediatric Immunology/Allergy Clinic, E Wolfson Medical Center, for suspected food allergy were enrolled in the study. Relevant medical data were gathered from the medical records, including the age of the child at the time of the first visit, suspected food allergens, and clinical manifestation of food allergy (cutaneous: urticaria, angioedema, and exacerbation of atopic dermatitis; respiratory: cough, wheezing, and rhinitis; and gastrointestinal: vomiting, diarrhea, colitis, dehydration, and anaphylaxis). We defined

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anaphylaxis as a severe life-threatening systemic reaction involving more than 1 organ system. The atopic status of patients and their first-degree relatives was investigated. Atopic manifestations included asthma/bronchitis, atopic dermatitis, food allergy, and allergic rhinitis. We rated the atopic background by using a scoring system. Each atopic manifestation in the child or his or her first-degree relatives was assigned 1 point. We rated the resulting total score of all these values as 0 for no atopic background, 1 for weak atopic background, 2 to 3 for moderate atopic background, and 4 to 7 for strong atopic background. Results of skin prick tests (SPTs), specific IgE measurements, and open oral food challenges were recorded.

Non-IgE-mediated milk/soy allergy was diagnosed in infants hospitalized in the pediatric department because of gastrointestinal symptoms, such as colitis, vomiting, diarrhea, and failure to thrive together with negative SPT reactions or in vitro specific IgE values. All of them recovered after substitution of an extensively hydrolyzed formula.

During 6 months in 2007, parents of children with confirmed food allergy were surveyed by telephone, and detailed questionnaires were completed by a single physician (D.A.). Missing clinical and epidemiologic data were completed, and information on the long-term course of the food allergy was obtained. We tested whether reintroduction of the suspected food allergen produced similar or new adverse reactions or alternatively was tolerated. New atopic manifestations and the occurrence of new food allergens were recorded. This study was approved by the institutional ethics committee of E Wolfson Medical Center, and oral informed consent was obtained from all parents or legal guardians.

Specific IgE Antibodies

Levels of specific IgE antibodies to relevant food allergens were evaluated using an advanced immunoassay system (IMMULITE 2000; Diagnostic Products Corp, Los Angeles, California). A positive value was determined to be 0.35 kU/L or higher.

SPT

Commercial extracts (Center Laboratories, Port Washington, New York) of the most common allergens (cow's milk, egg, sesame, wheat, peanut, soy, and fish) and any other foods suspected by history were used. Positive (histamine, 1 mg/mL) and negative (50% glycerosaline) controls were applied using the same technique. The SPT results were interpreted as positive when the wheal diameter was at least 3 mm.

Oral Challenge

An open oral food challenge was performed using incremental doses of the suspected food at 20-minute intervals up to a regular-sized dish. This was performed in a hospital set-up unit, which is fully equipped for cases of anaphylaxis. The patients were observed closely during the challenge and for 2 hours afterward.

Data Analysis

Data were recorded in a spreadsheet (Excel; Microsoft Corp, Redmond, Washington). For continuous variables, such as age, descriptive statistics were calculated and are reported as mean (SD). Categorical variables, such as sex and the presence of specific medical conditions, are described using frequency distributions. Statistical significance was analyzed using the Fisher exact test.

RESULTS

We identified 234 children with suspected food allergy. Fifty-four children (23%) were found not to have food allergy according to medical history, physical examination, and SPT findings, leaving 180 of 234 children (77%) with confirmed food allergy. These children were found to have 283 allergies: milk ($n = 125$), eggs ($n = 71$), sesame ($n = 30$), soy ($n = 23$), peanuts ($n = 14$), tree nuts ($n = 9$), fish ($n = 3$), beef and chicken ($n = 2$), and other foods (especially fruits such as peach, pineapple, and strawberry) ($n = 6$) (Table 1). One hundred seven children (59%) were allergic to only 1 food, 54 (30%) to 2 foods, and 19 (11%) to 3 or more foods.

Table 1. Natural History of Food Allergy in Pediatric Patients in Israel

Food allergen	Allergic cases, No.	Age at allergy onset, mean (SD), y	Age at allergy resolution, mean (SD), y	Resolved cases, No. (%)
Milk				
IgE mediated	86	0.3 (0.22)	2.0 (1.13)	32 (37)
Non-IgE mediated	39	0.22 (0.21)	1.4 (0.73)	35 (90)
Subtotal	125	0.34 (0.8)	1.7 (0.99)	67 (54)
Soy	23	0.18 (0.18)	1.9 (1.15)	19 (83)
Eggs	71	0.95 (0.77)	2.4 (0.91)	38 (54)
Sesame	30	1 (0.9)	2.8 (0.77)	9 (30)
Peanuts	14	0.93 (0.4)	2.0 (0.42)	3 (21)
Tree nuts	9	2.4 (1.35)	NR	0
Chicken and beef	2	0.67 (0.32)	2.0	1 (50)
Fish	3	0.95 (0.3)	1.8	1 (33)
Other	6	1.3 (1.07)	2.0	1 (17)

Abbreviation: NR, not relevant.

Fifty-two patients (29%) were diagnosed as having atopic dermatitis, 76 (42%) as having wheezing/asthma, and 38 (21%) as having allergic rhinitis. Mean age at food allergy occurrence matched the age at first consumption of the foods.

The children were followed up in the outpatient clinic for a mean of 4.7 years (minimum, 1 year). In 139 of 283 cases (49%) the allergy had resolved, in 93 (33%) it still existed, and in 51 (18%) it was not clear whether the allergy had been resolved (eg, patients who were lost to follow-up or were not rechallenged).

CMA

Of 125 patients with CMA, 86 (69%) were IgE mediated (group 1) and 39 (31%) were non-IgE mediated (group 2). The clinical presentation included gastrointestinal symptoms in 55% (including all group 2 patients), urticaria in 29%, anaphylaxis in 28%, angioedema in 11%, and respiratory symptoms in 0.8%. The CMA resolved in 67 children (54%), but according to groups there was a significant difference (Table 1). The CMA resolved in 35 of 39 group 2 patients (90%) at an average age of 1.4 years compared with only 32 of 86 group 1 patients (37%) at a mean age of 2.0 years ($P < .001$). Patients in group 1 had a more atopic background than did group 2 ($P < .003$).

Soy Allergy

Soy allergy was found in 23 children. Twenty-one (91%) of them also had CMA, and 2 were allergic to soy only. Clinical manifestations included gastrointestinal symptoms in 87%, urticaria in 9%, and anaphylaxis in 4%. The frequency of children with CMA and soy allergy in group 2 (10 of 39; 26%) was higher than that in group 1 (11 of 86; 13%). In 19 of 23 children (83%), the soy allergy resolved at an average age of 1.9 years (Table 1).

Sesame Allergy

Thirty children had allergy to sesame. In one-third of them the allergy presented as anaphylaxis. Other presentations included urticaria in 56%, angioedema in 7%, respiratory symptoms in 3%, gastrointestinal symptoms in 7%, and others in 7%. Most of the children with sesame allergy were found to have an atopic background (strong in 40%, moderate in 33%, weak in 7%, and no atopic background in 20%). Five children (17%) had a first-degree relative with sesame allergy. In only 9 patients (30%) the allergy had resolved at an average age of 2.8 years (Table 1).

DISCUSSION

Cow's milk is the most common cause of food allergy in infancy. It is estimated that CMA affects 2% to 3% of children, of whom 50% to 60% are IgE mediated.^{16,18,19} Of 125 children with CMA, 86 (69%) were IgE mediated. This relatively high rate of IgE-mediated allergy is probably biased because this study includes children referred to the allergy clinic by primary care physicians. Non-IgE-mediated allergic patients are often managed successfully by practicing pediatricians or gastroenterologists. During follow-up, we

found that non-IgE-mediated CMA tends to be outgrown more often ($P < .003$) and earlier (mean, 1.4 vs 2 years) than IgE-mediated allergy. This tendency has been previously described.^{15,16,20} In addition, we showed, similar to other studies,^{21–23} a strong, statistically significant association between IgE-mediated milk protein allergy and atopic background.

Recently, Skripak et al¹⁵ reported their results on the natural history of IgE-mediated milk allergy in the largest cohort of children. They found that rates of resolution were 19% by the age of 4 years, 42% by the age of 8 years, 64% by the age of 12 years, and 79% by the age of 16 years, emphasizing that the prognosis seems to be significantly worse than what has been previously reported. In contrast, Host and Halken¹⁶ found that 75% of children with IgE-mediated milk allergy were tolerant by the age of 3 years. This discrepancy could be explained, at least partially, by the difference in the study populations: referrals to a tertiary care center, which potentially represents patients with more severe allergy,¹⁵ compared with unselected patients with milk allergy.¹⁶

The present population, which was based on referrals to a secondary care center, probably represents a different type of population with CMA. The atopic status of these patients, as reflected by the co-appearance of atopic dermatitis, wheezing/asthma, and allergic rhinitis, was lower than that in the population of Skripak et al.¹⁵ These differences might explain the present results.

There is a clear association between soy allergy and CMA in the present patients. We found soy allergy in 23 children, 21 of whom were also allergic to milk. We showed that the prevalence of soy allergy in IgE-mediated CMA (11 of 86; 13%) is consistent with previous studies, and the prevalence in non-IgE-mediated allergy is lower than traditionally perceived (25% instead of 50%).²⁴ This discrepancy may reflect, again, the bias in the present population study because it is based on referrals to an allergy clinic, although other have reported findings similar to ours.^{24,25} Similar to non-IgE-mediated CMA, most cases resolved within 2 years.

Sesame is the third most common food allergen in Israel.^{13,14} We found 30 of 180 children (17%) to be allergic to sesame, whereas only 14 of 180 (8%) were allergic to peanuts. Peanut is a major allergen in North America and in parts of Europe, whereas sesame allergy is less common.^{26,27} In addition, a large portion of the present sesame-allergic patients (10 of 30; 33%) presented initially with anaphylaxis. Because of the major importance of sesame as a food allergen in Israel, we attempted to further characterize this group of patients. The average age at sesame allergy presentation was approximately 1 year, matching the first exposure to this food item in Israel. We found that most children with sesame allergy had personal and familial atopic backgrounds. In addition, we found that 17% of sesame-allergic patients had first-degree relatives who were also allergic to sesame. In 1 family, we identified as many as 3 sesame-allergic siblings (IgE mediated). Two of them had anaphylactic reactions to sesame. In a previous study,¹³ we showed that in 3 of 23

patients (13%), the allergy resolved during follow-up, but the time was too short for any definite conclusion. Cohen et al²⁸ followed 45 sesame-allergic patients for an average of 6.7 years and showed that tolerance developed in only 9 (20%). The median age at tolerance was 4.4 years.²⁸ In the present study, in 9 of 30 children (30%), the allergy resolved at an average age of 2.8 years.

In conclusion, CMA was the most prevalent allergy in this population, with early resolution occurring primarily in non-IgE-mediated allergy, as shown in previous studies. We found that most soy allergy in the present population was non-IgE mediated, presented with gastrointestinal manifestations, and tended to resolve within 2 years. Sesame allergy was one of the most frequent in this cohort, was IgE mediated, and tended to resolve in only a few patients with follow-up.

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